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Juvenile idiopathic arthritis-associated uveitis

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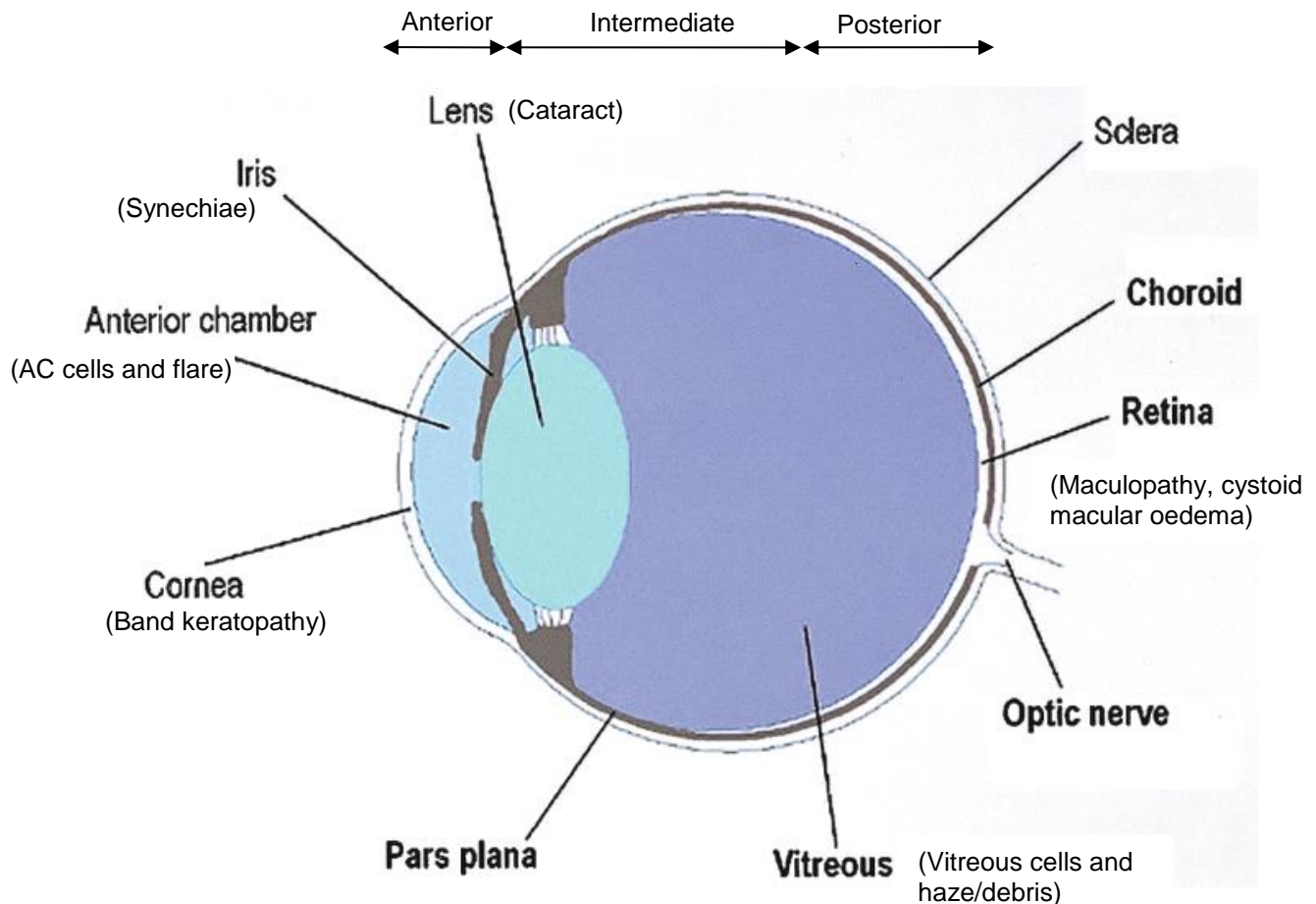
ABSTRACT

Juvenile idiopathic arthritis (JIA) is the commonest rheumatic disease in children and JIA-associated uveitis its most frequent extra-articular manifestation. The uveitis is potentially sight-threatening and so carries a considerable risk of morbidity with associated reduction in quality of life. The commonest form of uveitis seen in association with JIA is chronic anterior uveitis which is almost always asymptomatic in the initial stages. Therefore, screening for JIA-associated uveitis in at-risk patients is essential. The aim of early detection and treatment is to minimise intra-ocular inflammation and avoid complications leading to visual loss, which can result from both disease activity and medications. The sight-threatening complications of JIA-associated uveitis include cataracts, glaucoma, band keratopathy and macular oedema. There is increasing evidence for the early introduction of systemic immunosuppressive therapies in order to reduce topical and systemic glucocorticoid use. A recently-published randomised controlled trial of adalimumab in JIA-associated uveitis now provides convincing evidence for the use of this biologic in patients who fail to respond adequately to methotrexate. Tocilizumab and abatacept are being investigated as alternatives in children inadequately treated by anti-tumour necrosis factor drugs.

INTRODUCTION

Uveitis is a condition characterised by inflammation of the uveal components of the eye, namely the iris, choroid and retina.(1, 2) Classification has been defined in terms of the anatomy and time course of disease according to the Standardisation of Uveitis Nomenclature (SUN) international working group.(3, 4) Anatomically it can be described as anterior, intermediate, posterior or panuveitis (Figure 1). Uveitis onset may be sudden or insidious and its duration limited (≤ 3 months) or persistent (> 3 months).(3) The temporal pattern is described as acute (sudden onset and limited duration), recurrent (repeated episodes separated by periods of inactivity without treatment ≥ 3 months in duration) or chronic (persistent uveitis with relapse in < 3 months after discontinuing treatment). Uveitis can also be classified by aetiology into infectious and non-infectious.

Figure 1: Cross-section of eye showing areas affected in anterior, intermediate and posterior uveitis and potential complications (in brackets). Permission obtained from Wiley © Hughes, E.H. & Dick, A.D. The pathology and pathogenesis of retinal vasculitis. *Neuropathol. Appl. Neurobiol.* **29**, 325–340 (2003).(5)



In children with rheumatological disease, uveitis is seen associated with JIA, juvenile sarcoidosis / Blau syndrome and Behçet's disease.(6) The commonest form of uveitis is the chronic anterior type associated with juvenile idiopathic arthritis (JIA), and this will be the main focus of this review. This form of uveitis, which is usually asymptomatic, is most frequently associated with oligoarticular and rheumatoid factor (RF) negative polyarticular categories of JIA. Acute anterior uveitis, which often presents with a painful, red eye, can also occur in JIA, and is usually associated with enthesitis-related arthritis (ERA) and HLA-B27 positivity. If inadequately treated, JIA-associated uveitis (JIA-U) can lead to ocular complications, including glaucoma, cataracts, band keratopathy and persistent cystoid macular oedema, and can ultimately result in visual impairment and blindness.(7) Management of JIA-U involves use of both topical and systemic agents with clinical trials of biologic agents recently completed or underway.(8, 9)

EPIDEMIOLOGY

Children represent approximately 5-10% of all patients with uveitis (10). The overall incidence of uveitis in the childhood population, reported in a study from Finland, was 4.3 per 100,000/year and prevalence of 27.9 per 100,000 (11). Among all causes of paediatric uveitis, when stratified by aetiology, the prevalence of JIA-U ranged from 15-67% across centres in Europe, North America and Israel (10, 12-15). In a cohort of 642 children with uveitis in Tamil Nadu, India, infectious uveitis was most common representing 54.9%, followed by idiopathic and non-infectious at 32.5% and 12.6% respectively (16). It should be noted that uveitis can precede a diagnosis of arthritis in 3-7% of children with JIA (17) and thus children presenting with uveitis need careful assessment for underlying systemic or infectious disease.

How common is uveitis associated with JIA?

In patients already known to have JIA, estimates of prevalence of uveitis range from 11.6% (18) to 30% (19) although overall it appears to be decreasing over the past decade. A longitudinal cohort study conducted in Nordic countries prospectively followed 435 children diagnosed with JIA in 1997-2000 for a median of 96 months (20). Uveitis developed in 89 (20.5%) children. No patients with systemic or RF-positive JIA developed uveitis. The frequencies of chronic uveitis in other categories were: 35.7% in juvenile psoriatic arthritis, 22.5% in RF-negative polyarticular, 20.5% in extended oligoarticular, 19.1% in persistent oligoarticular, 19.0% in undifferentiated and 8.3% in ERA. Regarding disease pattern, the majority (80 children) had chronic uveitis while the remaining 9 patients had acute uveitis, all but one of whom had ERA. In another study where 13.1% of 1081 JIA patients developed uveitis, chronic anterior uveitis was also predominant (68.3%) (21). However, acute anterior disease (16.2%), recurrent anterior disease (12%) and panuveitis (3.5%) were also encountered.

What are the risk factors for development of uveitis in JIA?

Several risk factors for JIA-U have been identified. These include age of onset, gender, JIA category, and ANA and HLA-B27 positivity (7, 17, 19, 22, 23). A younger age, female gender, oligoarticular disease and presence of ANA are risk factors for chronic anterior uveitis. In contrast, being male with ERA and HLA-B27 predispose to acute anterior uveitis.

The interaction between individual risk factors is likely to be inter-dependent and complex. In a retrospective study of 1047 patients with JIA, the risk of developing uveitis was age-dependent in girls, but not boys (24). This finding seems to have been confirmed by the Nordic longitudinal study in which the median age at onset of arthritis in girls with uveitis was 3.4 years versus 6.8 years in girls without uveitis ($p < 0.001$) (20). The difference in age

at onset in boys was not significant ($p=0.39$). The study also identified anti-histone antibodies (AHA) ≥ 15 U/mL as a significant predictor of uveitis, but only in girls and not boys.

The impact of ethnicity on JIA-U is unclear. Early studies identified JIA-U in many different ethnic groups and suggested ethnicity did not play a role (25). More recent studies have suggested that those of European descent are at increased risk of JIA-associated uveitis compared to the at-risk local population (26).

When do children with JIA develop uveitis?

As discussed above, uveitis may precede arthritis in 3-7% of children with JIA. In the Nordic study, uveitis develops at a median interval of 0.8 (range -4.7 to 9.4) years after onset of arthritis. A single centre study conducted in Atlanta, USA, which included 52 children with JIA-U found that 24% were diagnosed with uveitis prior to arthritis, 22% within the first year after onset of arthritis and cumulatively 86% within 4 years of JIA diagnosis (23).

Sabri *et al* found that the mean time from onset of JIA to onset of uveitis was 1.8 years (21). Additionally, a recent study has suggested a biphasic course for the condition with a second peak of disease activity occurring around puberty (27) suggesting the need for vigilance in monitoring these patients over time.

PATHOGENESIS

The cause of the intraocular inflammation is not fully understood despite the strong association between JIA and uveitis being recognised for many years. There have been infrequent reports of familial cases of JIA-U.(28) However monogenic or Mendelian patterns of inheritance of JIA-U have not been seen (29), suggesting more complex genetic pathogenesis.

Uveitis in oligoarticular JIA has been linked with the HLA-DR5 haplotype and HLA-DRB*1104 allele; the combination of HLA-DRB1*1104 and HLA-DPB1*0201 is associated with a 7.7-fold increased risk of chronic uveitis (30, 31). The HLA-DR1 haplotype and HLA-DQA*0101 allele, in contrast, are protective. HLA-B27, which is seen more frequently in ERA, confers an increased risk of acute anterior uveitis (32). The associations with HLA type support the theory that JIA-U is an autoimmune disorder. It is thought that an immune response is triggered against intraocular antigens including S-arrestin (also known as retinal S-antigen), retinol-binding protein 3 (RBP3), and tyrosinase-related proteins (33).

Both B- and T-lymphocytes appear to be involved in pathogenesis of non-infectious uveitis. Immunohistochemistry of eye biopsies from patients with JIA-U showed a predominance of CD4⁺ T cells compared with CD8⁺ T cells and variable levels of CD20⁺ B cells.(34) CD4⁺ T cells of T helper type 1 (T_H1) and T_H17 subsets produce IFN- γ and IL-17, respectively (35-37). The pro-inflammatory effects of these cells are counterbalanced by CD4⁺ CD25⁺ FoxP3⁺ T regulatory (T_{REG}) cells and inducible T_{REG} cells. Although there is evidence for a role of T_H1, T_H17 and T_{REG} cells in uveitis pathogenesis, the exact roles of the T cell subsets in the course of disease has not been fully defined (34, 38, 39).

As noted previously, ANA positivity is a risk factor for JIA-U which raises the question of whether auto-antibodies are involved in the pathogenesis (40). Although a correlation between ANA and plasma cell infiltration in anterior uveitis has been reported, the specific intraocular antigens and whether ANAs are actually pathogenic are not clear (34). Potential targets of autoantibodies have been studied using immunofluorescence of tissue sections from eyes incubated with sera from patients with JIA (41). When using patient sera compared with controls, there appeared to be an increased frequency of antibodies against the iris and retina, but not the ciliary body. However, because blood samples were taken after uveitis was well established, it is not clear whether the anti-ocular antibodies are part of the

cause or consequence of disease. In future, serial serum samples taken from JIA patients before and after onset of uveitis could enable the potential prognostic significance of antibody binding to be investigated.

Macrophages, in addition to lymphocytes, are seen in biopsy samples of eyes with uveitis (34). Both cell types exert pro-inflammatory effects through secretion of cytokines and chemokines. In one study including children with JIA-U, levels of IL-2, IL-6, IL-13, IL-18, IFN- γ , TNF, soluble ICAM-1 (also known as CD54), CCL5 and CXCL10 in the aqueous humour were considerably higher than in controls without uveitis (42).

CLINICAL FEATURES

How does JIA-associated uveitis present?

In the case of acute anterior uveitis, presentation can be with overt symptoms (1). Typical features include photophobia, eye pain, redness, visual changes and headaches. However, chronic anterior uveitis, more commonly seen in JIA, is often completely asymptomatic. Therefore, regular screening for uveitis in patients with JIA is essential to detect clinically-silent, but potentially vision-threatening, disease. Younger children, in particular, may be unable to report reliably any visual changes, so the need for formal assessment of vision and the education of families of the importance of this is vital.

It is well-recognised that uveitis can develop before the onset of arthritis, and in these cases the eye inflammation may go unnoticed for a significant period (17, 20, 23). In all children diagnosed with non-infectious uveitis, features of systemic disease, including JIA, should be actively sought at the time of diagnosis and the potential of an underlying condition revisited over subsequent months.

DIAGNOSIS AND SCREENING

Which patients should undergo screening for uveitis?

All patients at risk of JIA-U should be screened for uveitis. Screening guidelines are available in several countries including the UK (43), Germany (44) and USA (45, 46). The UK guidelines are summarised in Box 1. Consensus standards in the UK recommend first ophthalmological assessment to take place within 6 weeks of JIA being diagnosed or suspected (47), underlining the importance of prompt diagnosis and treatment. Systemic immunosuppression used to treat arthritis may be controlling uveitis even in patients with no previous intra-ocular inflammation. Therefore, UK guidelines recommend increasing frequency of screening to 2-monthly for the first 6 months after stopping methotrexate or other systemic treatment (43).

Referral

- Patients should be referred at time of diagnosis, or suspicion, of JIA

Initial screening examination

- Should occur as soon as possible and no later than six weeks from referral
- Symptomatic patients should be seen within a week of referral

Ongoing screening

- Screening at two monthly intervals from onset of arthritis for six months
- Followed by 3-4 monthly screening for time outlined below:
 - Oligoarticular JIA, psoriatic arthritis and enthesitis related arthritis irrespective of ANA status onset under 11 years

Age at onset	Length of screening
< 3 years	8 years
3-4 years	6 years
5-8 years	3 years
9-10 years	1 year

- Polyarticular, ANA +ve JIA, onset <10 years

Age at onset	Length of screening
< 6 years	5 years
6-9 years	2 years

- Polyarticular, ANA –ve JIA, onset <7 years
Five year screening for all children
 - Systemic JIA and rheumatoid factor +ve polyarticular JIA
Uveitis risk very low, however diagnostic uncertainty in the early stages and overlap of symptoms may mean initial screening is indicated
 - All categories, onset >11 years
One year screening for all children
 - After stopping immunosuppression eg methotrexate
Two monthly screening for six months, then revert to previous screening frequency as above
 - After discharge from screening
Patients should receive advice about regular self-monitoring by checking vision unilaterally once weekly and when to seek medical advice
Screening may need to continue indefinitely in situations where young person may be unable to detect a change in vision or be unwilling to seek re-referral
Annual check by optometrist as a useful adjunct

Box 1: British Society for Paediatric and Adolescent Rheumatology/ Royal College of Ophthalmology guidelines for uveitis screening in JIA (43).

How is JIA-associated uveitis diagnosed and monitored?

Screening of children with JIA for uveitis involves a combination of age-appropriate visual acuity (VA) testing, measurement of intraocular pressure and slit lamp examination. The latter allows examination of the anterior and posterior chambers as well as the retina. A diagnosis of uveitis is made based on features of inflammation on slit lamp examination which include cells in the anterior chamber (AC) (1) and AC flare resulting from protein leakage into the AC due to breakdown of the blood–aqueous humour barrier (48). Intraocular inflammation is graded according to the SUN criteria which take into account AC cells, AC flare, vitreous cells, and vitreous haze or debris (Box 2). The criteria also provide definitions of improvement and worsening of the condition (Box 2) allowing reproducible assessment and monitoring of uveitis activity. It is important to note that 0.5+ AC cells should not be considered inactive uveitis (3).

Grading scheme for anterior chamber cells

Grade	Cells in field*
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Grading scheme for anterior chamber flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Activity of uveitis terminology

Term	Definition
Inactive	Grade 0 cells†
Worsening activity	Two step increase in level of inflammation (e.g. anterior chamber cells, vitreous haze) or increase from grade 3+ to grade 4+
Improved activity	Two step decrease in level of inflammation (e.g. anterior chamber cells, vitreous haze) or decrease to grade 0
Remission	Inactive disease for ≥ 3 months after discontinuing all treatments for eye disease

*Field size is 1mm by 1mm slit beam

†Applies to anterior chamber inflammation

Box 2: Standardisation of Uveitis Nomenclature (SUN) criteria for uveitis activity

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Both inflammation and topical glucocorticoids used as treatment increase the risk of intraocular hypertension and glaucoma. Therefore, regular measurement of intraocular

pressure is important in patients with JIA-U. The risk remains, despite control of active inflammation, as illustrated by one study showing the first measurement of raised intraocular pressure at a time when the disease was inactive in 60% of eyes (49).

The assessment of VA provides a measure of both disease activity and visual damage resulting from both chronic disease activity and failure or complications of treatment.(2) Guidelines for measuring outcome in JIA-U, which include assessment of VA as a key component, have been developed (50). This should be best corrected visual acuity (BCVA) using age-appropriate tests recorded monocularly and binocularly and converted to logMAR. Several complications of JIA-U can contribute to visual loss. These include glaucoma, hypotony, cataract, band keratopathy, posterior synechiae, macular oedema, epiretinal membrane, and optic disc oedema.

TREATMENTS

Early detection, through rapid referral and regular screening, and appropriate assessment of disease activity are key to the management of JIA-U. This relies on effective communication between paediatric rheumatologists and ophthalmologists which may be helped by organisation of multi-disciplinary clinics. The target of effective treatment is to achieve 0 cells in the anterior chamber (SUN AC cell grade 0) in both eyes (51). Practical management protocols have recently been published both by our group in Bristol, UK (52) and an interdisciplinary panel from Spain (51). Figure 1 shows a modified algorithm based on consensus guidelines for management of chronic anterior uveitis (51-53).

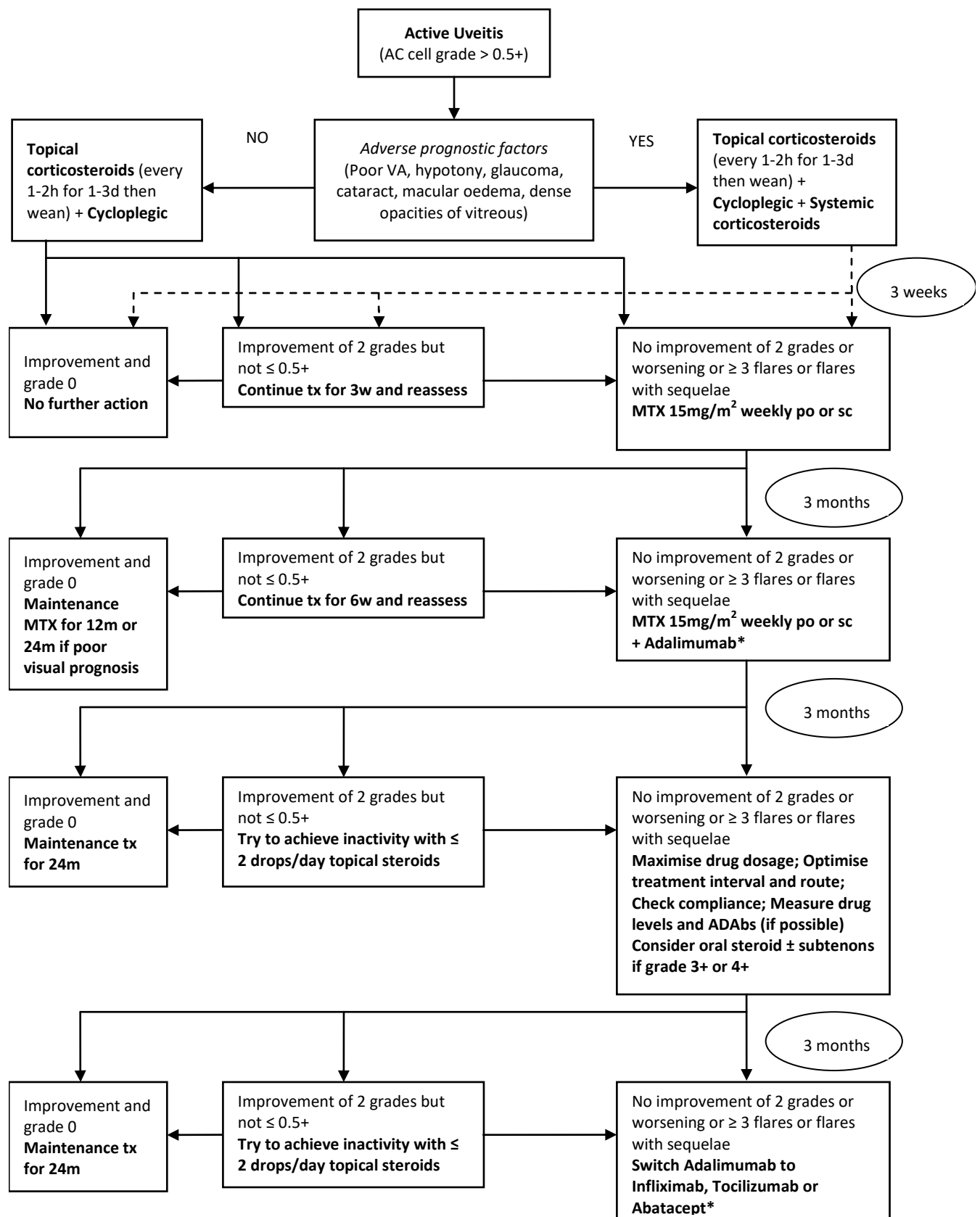


Figure 1: Treatment algorithm for juvenile idiopathic arthritis-associated uveitis

[Adapted with permission from Springer © Bou, R. *et al. Rheumatol Int* **35**, 777-785 (2015) [36] and from Springer © Heiligenhaus, A. *et al. Rheumatol Int* **32**, 1121-1133 (2012) [38]]

At all stages aim to minimise topical steroid to ≤ 2 drops/day while maintaining AC cell grade $\leq 0.5+$

* Mycophenolate mofetil (MMF) is a potential alternative to a biologic drug if there is active uveitis but no active arthritis

Legend: AC: anterior chamber, d: days, h: hours, m: months, MTX: methotrexate, po: by mouth, sc: subcutaneous, tx: treatment, VA: visual acuity, w: weeks

Guidelines on management of JIA-U advise that therapy is initiated when the AC cell grade is $> 0.5+$ (53). Treatment is also indicated when there is fibrin in the AC and keratocytic precipitates with corneal oedema and loss of VA. Failure to see improvement in inflammation or presence of poor prognostic factors are indications for intensification of immunosuppressive treatment. Poor prognostic factors are: impaired initial vision, cataract, glaucoma, ocular hypotony, dense vitreous body opacification and macular oedema. Band keratopathy, synechiae, cataract and glaucoma alone, in the absence of active uveitis, do not require anti-inflammatory treatment (53).

What are the first- and second-line treatments for JIA-associated uveitis?

The first-line treatment for both acute and chronic anterior uveitis is topical glucocorticoids (53-55). The primary indication for systemic immunosuppression with one of the DMARDs is failure of adequate control of inflammation after 3 months of topical treatment, particularly with > 3 drops daily (53). Methotrexate (MTX) remains the first second-line therapy after topical glucocorticoids. The use of, and evidence for, local and systemic glucocorticoids, cycloplegics and non-biologic DMARDs have been reviewed by us recently (1, 2) and so are not discussed in detail here. Table 1 summarises the range of non-biological immunosuppressants used to treat JIA-U, their doses and evidence base. Current treatment

algorithms recommend that if there is worsening disease or failure to achieve AC cell grade 0 after 3-4 months on MTX, then a biologic drug is added (51, 56)

Table 1: Non-biological immunosuppressants used in treatment of JIA-associated uveitis

Drug name	Mechanism	Dosage and route	Common side effects	Evidence	Key references
Methotrexate	Cellular adenosine release(57)	10-15mg/m ² po or sc once weekly	GI discomfort, nausea, elevated liver enzymes	Systematic review and meta-analysis of retrospective case series (n=135): improvement in 73%	(58)
Azathioprine	Purine nucleoside analogue, inhibits DNA replication	1mg/kg od, increasing to maximum 3mg/kg od	GI discomfort, bone marrow suppression, liver impairment	Retrospective case series (n=41): uveitis inactivity in 61.5% as initial monotherapy; 66.7% as combination therapy	(59)
Mycophenolate mofetil	Inhibitor of inosine-5-monophosphate dehydrogenase	300mg/m ² bd, increasing to 600mg/m ² bd	GI discomfort, leukopenia, hair loss	Several retrospective case series (n=17, 52 and 85; not all with JIA, variable outcome measures): response in 55-88%	(60-62)
Ciclosporin	Calcineurin inhibitor blocking T cell proliferation	2.5-5mg/kg/day in 2 doses	GI disturbance, hypertension, renal and liver dysfunction, lipid abnormalities	Retrospective case series (n=82 and 14): uveitis inactivity in 24% as monotherapy, 48.6% as combination therapy	(63, 64)
Tacrolimus	Calcineurin inhibitor blocking T cell proliferation	50-150 microgram/kg bd	GI disturbance, hypertension, renal and liver dysfunction, lipid abnormalities, blood disorders	Retrospective case series (n=62, mostly adults with idiopathic uveitis): permitted glucocorticoid tapering and improved visual acuity	(65)

Legend: bd- twice daily; GI- gastro-intestinal; od- once daily; po- by mouth; sc- subcutaneous.

Which biologic drugs are effective in JIA-associated uveitis?

Over the past decade, randomised controlled trials (RCTs) of biologic agents have demonstrated their efficacy in controlling joint disease in JIA (66). The same drugs have also been used in treatment of associated uveitis (Table 2).

Table 2: Biological immunosuppressants used in treatment of JIA-associated uveitis

Target	Drug name	Drug class	Dosage and route	Evidence	Key references
TNF α	Etanercept	Dimeric fusion protein	Not recommended for treatment of JIA-U	RCT: no more effective than placebo. Case reports of new uveitis on etanercept	(67, 68)
	Infliximab	Chimeric (mouse-human) mAb	6mg/kg IV initially, then 3-10mg/kg. 2 nd dose at 2 weeks, then every 4-8 weeks depending on response	Several case series showing efficacy	(67)
	Adalimumab	Fully human mAb	24mg/m ² sc q2w In practice, often 20mg sc q2w (body weight <30kg), 40mg sc q2w (body weight \geq 30kg)	Several case series showing efficacy. RCT demonstrated greater efficacy of adalimumab vs placebo.	(8, 67, 69)
	Golimumab	Fully human mAb	50mg sc q4w	Case series (n=3) showing efficacy	(70)
IL-6	Tocilizumab	Humanised mAb	10mg/kg (body weight <30kg), 8mg/kg (body weight >30kg) IV q4w	Several case series showing efficacy. Phase II trial in progress	(9, 71-75)
CD80/86 (CTLA4)	Abatacept	Fully human fusion protein	10mg/kg IV at weeks 0, 2, 4 then q4w	Case series (n=7 and n=2) showing efficacy. Lack of sustained response in severe uveitis (n=21)	(76-80)
CD20	Rituximab	Chimeric (mouse-human) mAb	375mg/m ² or 750mg/m ² IV, two doses 2 weeks apart	Case series (n=10 and n=8 with long-term follow-up) showing efficacy in most patients	(81-83)

Legend: CTLA-4- cytotoxic T-lymphocyte-associated antigen 4; IL- interleukin; IV- intravenous; JIA-U- juvenile idiopathic arthritis-associated uveitis; mAb- monoclonal antibody; od- once daily; ow- once per week; q2w- every 2 weeks; q4w- every 4 weeks; RCT- randomised controlled trial; sc- subcutaneous; TNF- tumour necrosis factor.

Adalimumab

The greatest evidence, previously derived from cohort studies (67) and recently from an RCT, supports the use of adalimumab in treatment of JIA-U. A multi-centre, double-blind, RCT of adalimumab versus placebo was designed to assess the efficacy and safety of the drug used to treat active JIA-U in children and adolescents aged 2 years and older (8). All recruited patients had active uveitis despite glucocorticoid and MTX therapy for at least 12 weeks and continued on a stable dose of oral or subcutaneous MTX throughout the study. Eligible patients were randomised in a 2:1 ratio to receive adalimumab (20 mg in those weighing < 30 kg or 40 mg in those \geq 30 kg) or placebo subcutaneously every 2 weeks. The primary end point was the time to treatment failure (assessed by a multicomponent intraocular inflammation score). Secondary end points included use of topical and systemic steroids, flare of uveitis, flare of JIA, Juvenile Arthritis Disease Activity Score (JADAS), minimal disease activity, the American College of Rheumatology (ACR) paediatric core outcome set variables and health-related quality of life. All adverse events (AEs) were reported regardless of severity or perceived association with the trial intervention. Patients were reviewed at 4, 8 and 12 weeks and then every 12 weeks until 18 months or until treatment failure, after which they continued to be seen for another 6 months. The targeted recruitment was 114 patients to achieve 80% power. However, the study was stopped early at the recommendation of the data and safety monitoring committee after randomising 90 patients (60 to adalimumab and 30 to placebo) when a pre-specified stopping boundary ($p < 0.0001$) was reached for the primary end point. The time to treatment failure was significantly delayed by addition of adalimumab to MTX versus placebo (hazard ratio of 0.25; 95% CI 0.12-0.40; $p < 0.0001$). Treatment failure occurred in 27% of patients in the adalimumab group versus 60% in the placebo group. A significantly greater proportion of patients on adalimumab were able to reduce topical steroids. In post hoc analysis, 57% in the

adalimumab group and 17% in the placebo group were classified as having a response. There was no significant difference between the groups regarding health-related quality of life. A total of 588 AEs were noted in 88% of patients on adalimumab and 83% on placebo, with minor infections and respiratory disorders being the most common. Serious adverse events (SAEs) were more common in the adalimumab group (0.29/patient-year (PY) versus 0.19/PY) as were AEs (10.07/PY versus 6.51/PY).

Based on the above RCT, adalimumab is now the biologic drug with the strongest level of evidence of efficacy for treatment of JIA-U when added to MTX. However, there remain a group of patients whose uveitis does not respond to adalimumab or who flare despite achieving initial control. In one retrospective study, 59 of 68 patients who were treated with adalimumab achieved response within 6 months (84). However, 8 of the initial responders subsequently discontinued the treatment because of reactivation of uveitis.

Other anti-TNF agents

A double-blind RCT of etanercept in 12 patients with JIA-U showed no difference between the drug and placebo (68). The study, with this small number of patients, was powered to detect a difference only if greater than 70 percentage points between treatment arms. Several studies have reported new onset of uveitis or flares while on etanercept (85-87). Although there is not clear evidence that etanercept causes uveitis, and it may occur while on other drugs, data from national registries show that etanercept is associated with a greater number of uveitis cases than adalimumab or infliximab (88). Etanercept is not recommended in patients with JIA-U.

A meta-analysis including 229 children with JIA-U has shown that adalimumab and infliximab have similar efficacy and both are superior to etanercept (67). However, during 40 months' follow-up, uveitis more commonly remained in remission in those treated with adalimumab compared with infliximab (60% vs 18.8% respectively) (89). A small case series has reported that switching between anti-TNF agents, particularly from infliximab to adalimumab, can regain control of uveitis (90).

Tocilizumab

Use of tocilizumab, a fully humanised anti-IL6R antibody, for treatment of JIA-U was previously reported only in small case series (71, 72). Within the last two years, two larger, multi-centre, retrospective cohort studies including 17 and 25 patients respectively have been published (74, 75).

Tappeiner *et al.* reported experience treating 17 patients (14 female; mean age 15.3 years, range 7-30 years) with severe and refractory active JIA-U with tocilizumab (74). All had previously failed glucocorticoids, non-biologic DMARDs and at least one anti-TNF. The median time between onset of uveitis and starting tocilizumab was 10 years (range 3.9-27 years). Thirteen (76.4%) had secondary ophthalmic complications at baseline. Intravenous tocilizumab (8 mg/kg body weight) was administered at 4-weekly intervals. Uveitis activity using SUN classification, BCVA, optical coherence tomography (OCT), intraocular complications and arthritis activity were recorded at baseline and 3, 6, 9 and 12 months. In patients with bilateral uveitis, results for the eye with the higher AC cell grade were reported. Any changes in treatment were at the discretion of the managing physician.

Uveitis inactivity (AC cell grade = 0) was achieved in 4/17 (23.5%) at 3 months, 5/14 (35.7%) at 6 months, 5/9 (55.6%) at 9 months and 4/8 (50.0%) at 12 months. Ten patients showed inactivity for at least one visit but 7 patients had no response showed persisting activity throughout follow-up and 5 stopped treatment because of lack of efficacy. Cystoid macular oedema was present in 5 eyes at baseline and resolved in all with tocilizumab. Sparing of systemic corticosteroids or other immunosuppressive medications was possible in 13 patients, however in 6 of these uveitis subsequently recurred (n = 3) or worsened (n = 3). There was no significant change in BCVA between baseline and the end of follow-up but 4 patients developed new ocular complications. No SAEs requiring discontinuation of tocilizumab were reported.

As the authors point out, although tocilizumab seemed effective in some patients, it was a cohort with severe, refractory uveitis, many with long-standing, irreversible ocular damage. Use of tocilizumab much earlier in the disease course, after failure of the first anti-TNF or as the first biological DMARD, may show a higher response rate.

Calvo-Río *et al.* reported their experience with tocilizumab treating 25 patients (21 female; mean age 18.5 years, range 8-38 years; 47 affected eyes) with JIA-U refractory to glucocorticoids, non-biologic DMARDs and at least one biologic, in all cases including an anti-TNF. The median time between onset of uveitis and starting tocilizumab was 8.8 years (interquartile range [IQR] 2.0-16.5 years). Over half had complications at baseline including: cataracts (n = 13), glaucoma (n = 7), synechiae (n = 10), band keratopathy (n = 12), maculopathy (n = 9) and amblyopia (n = 5). Intravenous tocilizumab (8 mg/kg body weight) was administered at 4-weekly intervals in 21 patients, 2-weekly in two, 8-weekly in one and 2.9 mg/kg subcutaneously every week in one. Uveitis activity, using SUN classification, macular thickness using OCT, BCVA and corticosteroid-sparing effect were the outcome

measures recorded at baseline, 1 week and 1, 3, 6, and 12 months. For AC cells and vitreous haze, each patient was considered as an independent variable. Regarding BCVA and OCT differences, results were reported considering the number of affected eyes.

Improvement in uveitis activity (AC cell grade according to SUN definition) was achieved in 16% at 1 week, 40% at 2 weeks, 64% at 1 month, 68% at 3 months, 79.2% (19/24) at 6 months and 88.2% (15/17) at 12 months. Ocular remission was achieved in 19 (76%) of the patients with median follow-up of 12 months (IQR 6-24 months). Cystoid macular oedema improved in all 9 patients with this finding at baseline with significant reduction in macular thickness at 6 and 12 months. Significant decreases in daily median dose of prednisolone from 10 mg at baseline to 2.5 mg at 6 months and 0 mg at 1 year were reported. A statistically significant improvement in BCVA was observed from Snellen chart score $11.2 \pm 7.0 / 20$ at baseline to $12.8 \pm 6/4 / 20$ at 6 months. Tocilizumab was withdrawn because of AEs in two patients: severe autoimmune thrombocytopenia in one patient, and autoimmune anaemia and thrombocytopenia in another. A third patient had viral conjunctivitis and bullous impetigo which required temporary cessation of tocilizumab. One patient stopped treatment because lack of efficacy.

Overall, this study seems to report more favourable response to tocilizumab than that of Tappeiner *et al.* although there are some differences between the studies in whether certain outcomes were reported as per patient or per eye, and in the frequency/route of administration in a small number of patients. The median time between uveitis onset and starting tocilizumab was slightly shorter in the study of Calvo-Río *et al.* at 8.8 years versus 10 years but the proportion of patients with specific ocular complications at baseline was similar in the two studies.

Subcutaneous tocilizumab has been tested in clinical trials in adults with rheumatoid arthritis and shown to have comparable efficacy to intravenous administration with the benefit of self-administration and avoidance of more frequent hospital attendance (91). Clinical trials of subcutaneous tocilizumab in JIA are in long-term follow-up (92). A case series of 4 patients with JIA and uveitis, who switched from the intravenous route when their disease was in remission to subcutaneous treatment, reported that all patients experienced relapse within a few months of switching (93). Three patients suffered an ocular flare and two a joint flare; all stopped subcutaneous tocilizumab due to lack of efficacy.

Further study of the role of tocilizumab in treatment of JIA-U is required and the APTITUDE trial, an open-label study of subcutaneous tocilizumab for anti-TNF-refractory JIA-U is currently recruiting patients in the UK (9).

Other biologic drugs

Experience using abatacept and rituximab for treatment of JIA-U has been reported in case series (Table 2). Efficacy was seen in most patients although only small numbers have been reported.

When should treatment for uveitis be stopped?

The duration of maintenance therapy on biologic agents once uveitis is in remission is not clear. Consensus recommendations suggest continuing treatment for 24 months of inactive disease (51). One retrospective cohort study (n=50, 44% with JIA) has reported on uveitis reactivation after stopping infliximab (n=45) or adalimumab (n=5) (94). Of 19

patients who achieved remission and were subsequently withdrawn from anti-TNFs, 63.8% had reactivation within 12 months and there did not appear to be an association with duration of medication-induced remission. Another retrospective cohort study, which followed children with non-infectious uveitis after stopping systemic therapy, identified a higher probability of remaining in remission in those with idiopathic rather than JIA-associated uveitis, if inactivity was achieved within the first 6 months of systemic therapy and if it was achieved by an anti-TNF treatment (95).

Do biologic drugs cause uveitis?

More data are increasingly available on the safety of biologic drugs in JIA and rates of adverse events such as uveitis. Several studies have reported flares or new-onset uveitis while on etanercept (85-87). Evidence from national registries suggests that etanercept is associated with a greater number of uveitis cases than adalimumab or infliximab (88). However, no definite causative effect of etanercept can be proved from these retrospective observational studies and the prescribing pattern of the different anti-TNFs may be a confounding factor (96). A German registry study (n=3467 patients) suggested that in those patients with a known negative past history of uveitis the rate of a new uveitis event was 3.2/1000 patient years (PY) in the MTX group, 1.9/1000PY in the etanercept monotherapy group and 0.9/1000PY in the group on the combination of both (97). An observational study reporting adverse events in JIA patients receiving biologics in Finland (n=348 patients) reported a rate of new-onset uveitis of 0.8/100PY, 0.3/100PY and 0.5/100PY while on etanercept, infliximab and adalimumab respectively (98). The rates of uveitis flare were 2.8/100PY, 8.0/100PY and 3.8/100PY for each respective treatment. The authors suggest that the apparently higher rate of flare while on infliximab is because most patients with a

pre-existing diagnosis of uveitis were started on this drug during the observation period (1999-2009).

PROGNOSIS

Complications in JIA-U result both from the disease itself and its treatments. The condition remains a cause of blindness in children and visual loss may be present at first assessment with one study describing VA of 20/50 or worse in 40.3% and 20/200 or worse in 24.2% at presentation (99). A systematic literature review looking at outcomes in JIA-U showed an adverse visual outcome (VA < 20/40 both eyes together) in 9.2% of those with uveitis (7). The main complications were cataracts, glaucoma and band keratopathy occurring in 20.5%, 18.9% and 15.7% respectively.

One study focussing on long-term follow-up reported a cohort of 55 JIA-U patients diagnosed and treated between 1973 and 1982 (100). Seven years after uveitis onset, 42% had cataracts and 5% glaucoma. At 24 years, 51% had cataracts, 22% glaucoma and 49% had signs of active uveitis or were receiving topical glucocorticoids for recent flares. Similar persistence into adulthood of asymptomatic uveitis in almost half of patients with JIA-U was seen in a cohort of 19 subjects who were born in 1976-1980 (101).

What features predict more severe course and development of complications?

The risk factors for poor prognosis in JIA-U include: male gender; young age at onset of uveitis; short duration between onset of arthritis and development of uveitis; and presence of synechiae at first diagnosis of uveitis (102-104). A retrospective case series (n = 65) showed significantly worse VA in boys versus girls at 1 year and 3 year follow-up (105). Another study suggested that a shorter time interval between arthritis and uveitis onset is the

main predictor of severity of uveitis (106). Risk factors for visual loss, were examined in a retrospective study with 596 affected eyes (99). The overall incidence of visual loss to 20/50 or worse was 0.18/eye year (EY). The overall rate of developing a new ocular complication was 0.15/EY but significantly lower at 0.04/EY in those with no complications at baseline. The same study also showed bilateral uveitis, active uveitis ($\geq 1+$ AC cells or ≥ 0.5 vitreous haze), longer duration of uveitis, presence of posterior synechiae, abnormal intraocular pressure (IOP) and history of prior intraocular surgery were associated with worse vision during follow-up.

CONCLUSION AND FUTURE DIRECTIONS

Better understanding of the pathogenesis of JIA-U may help to identify biomarkers, either genetic or in plasma, which would allow stratification of patients to higher risk groups. These could be targeted with earlier and more aggressive therapy.

Key to improvement of therapies is the effective translation from bench to bedside (107). High quality evidence for efficacy and safety of novel treatments specifically within a JIA-U population is required.

JIA-U remains a challenge for paediatric rheumatologists and ophthalmologists with significant numbers of children still developing sight-threatening complications. Although understanding of the pathogenesis of non-infectious uveitis is growing, studies focussing specifically on JIA-U are generally lacking. Recent evidence-based guidelines have highlighted the importance of earlier use of systemic immunosuppression with steroid-sparing agents in cases of persisting uveitis activity. We now have increasing treatment

options, with an RCT of adalimumab now completed and clinical trials in progress of other biological agents for refractory cases. The identification of predictive biomarkers to help target the widening therapeutic armamentarium will be a key goal for the coming years.

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E. S. Sen performed a literature review and wrote the article. A. V. Ramanan made contributions to discussion of content and review/editing of the manuscript before submission.

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Competing interests statement

E. S. Sen declares no competing interests.

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